ReFlections

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Dr. Adela Osman,
Chief Medical Research Officer, South Africa
adela.osman@rgare.com

Dr. Daniel D. Zimmerman,
Senior Vice President, Chief Medical Director, Global Medical
dzimmerman@rgare.com

IN THIS ISSUE

FROM THE EDITORS

First and foremost, we sincerely hope this newsletter finds you and your families safe and healthy during these unprecedented and challenging times. It is also now, more than ever, that we realize the important role our industry plays in serving the financial needs of our clients and policyholders.

This is the 50th edition of *ReFlections*, RGA's global medical newsletter. It has been our pleasure to provide this essential service for the past 21 years and we look forward to continuing to do so for many years to come.

In this "golden" anniversary edition, we highlight two new authors as well as one who is well-known to *ReFlections* readers. To start off, new author Lauren Garfield, Ph.D., MPH, Underwriting Research Consultant, U.S. Mortality Markets, takes us through the complicated topic of head and neck cancers and further explores the impact of human papilloma virus (HPV) on many of these cancers. Next, Dr. Sheetal Salgaonkar, Vice President and Medical Director, Global Medical, RGA India, provides a deep dive into the important and growing world of hematopoietic stem cell transplantation. Last, new author Sharon Latocha, Senior Underwriting Consultant, RGA Australia, researches the emerging risk of *Candida auris* infections and their relevance to insurance medicine, underwriting, and claims.

The Longer Life Foundation (LLF) update is dedicated in its entirety to researchers who are on the front line of the COVID-19 battle. We highlight two former LLF grant recipients who share their current endeavors and how they hope to favorably impact the trajectory of the pandemic. LLF is proud to have supported their work in the past and salutes their ongoing efforts.

Please be safe and we wish you all good health.

Thank you,

Dan and Adela

HEAD AND NECK CANCERS: UPDATE 2020

Abstract

Head and neck cancers (HNCs) are defined as those of the upper aerodigestive tract, which includes the oral cavity, the mucosal lip, the oropharynx, the hypopharynx, the nasopharynx, the larynx, and the salivary glands. HNCs were the eighth most common cancers worldwide in 2018 and accounted for 3% of all cancer diagnoses and about 1.5% of cancer deaths in the U.S. alone. Up to an estimated 85% of all HNC risk today is due to smoking and other tobacco product use, and alcohol consumption is also an important independent risk factor. Human papillomavirus (HPV) is an emerging risk factor as well, specifically for oropharyngeal cancer, the most common type of HPV-associated cancer, which has patient demographics that differ substantially from those of non-HPV associated HNC cases. Survival rates for HNCs, according to Surveillance, Epidemiology, and End Results (SEER) data, show overall survival for localized cancers range from more than 90% for salivary gland and mucosal lip sites to closer to 60% for laryngeal and hypopharyngeal sites.

Several important changes were made in HNC staging in the AJCC Cancer Staging Manual, Eighth Edition, released by the American Joint Committee on Cancer on January 1, 2018. This article updates the reader on HNC and reviews the staging changes.

Epidemiology and Risk Factors

Head and neck cancers (HNCs) are specifically defined as cancers of the upper aerodigestive tract, which includes the oral cavity, the mucosal lip, the oropharynx, the hypopharynx, the nasopharynx, the larynx, and the salivary glands.[1] Globally, HNCs were the eighth most common cancer in 2018, accounting for 3% of all cancer diagnoses and 1.5% of cancer deaths in the U.S. alone.[2]

More than 90% of all HNCs are squamous cell carcinoma (SCC), arising in the mucosal surfaces lining the aerodigestive tract.[3] The oral cavity is the most common site of occurrence.[4, 5]

HNCs have several risk factors. The most common are:

- **Tobacco use.** Up to 85% of HNC risk is estimated to be due to smoking and other tobacco product use.[6] For heavy smokers, the risk of HNC is five to 25 times higher than it is for nonsmokers.[7] As global rates of smoking and tobacco use have declined, so have rates of tobacco-related HNC. This decline, however, has not been uniform. Rates have dropped mostly in North America and Western Europe,[8] but remain high in Eastern Europe and throughout Asia – especially in China, India, and Indonesia, where half of the world's male smokers currently reside.[9]

  Several modes of tobacco use specific to South and Southeast Asia may also be predisposing individuals to oral cancers, due to how they are used and the components with which tobacco is combined.[10] Use of betel quid, for example, is common in both regions as well as among

ABOUT THE AUTHOR

Lauren Garfield, Ph.D., MPH
Lauren.Garfield@rgare.com

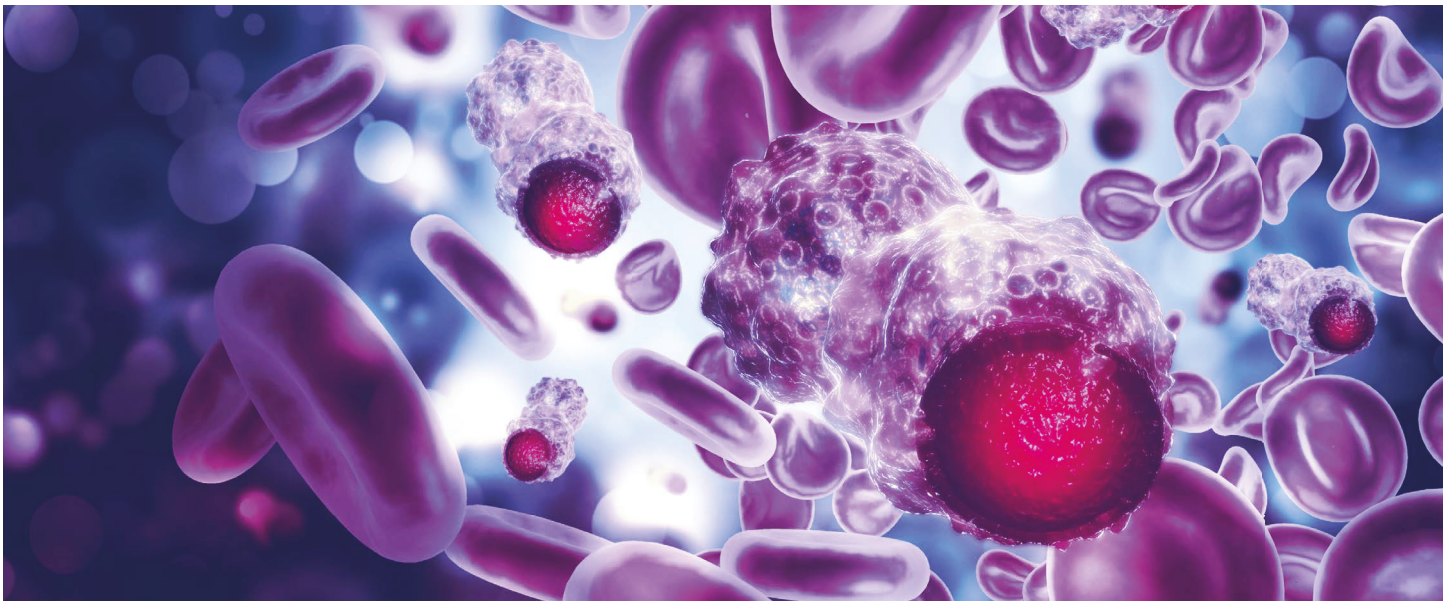
Lauren Garfield, Ph.D., MPH, is an Underwriting Research Consultant with RGA Reinsurance Company. Her work focuses on RGA's U.S. underwriting manuals. She is an epidemiologist and health outcomes researcher with a B.A. from Washington University in St. Louis and an MPH and Ph.D. from Saint Louis University School of Public Health. Before coming to RGA, Dr. Garfield completed postdoctoral research training in the Department of Psychiatry at Washington University School of Medicine in St. Louis and has also worked in several health analytics positions in U.S. companies. Her personal research interests are in mental and behavioral health.

populations that emigrated from these areas, and may be responsible for the high prevalence of oral cancer in these populations.[11] Betel quid use involves either chewing or placing between the lip and gum a packet consisting of areca nut, calcium hydroxide (slaked lime), betel leaf, tobacco, and various flavorings.[12] Several components of betel quid in addition to tobacco, such as areca nut, are known carcinogens (betel quid as well as areca nut are classified as Group I carcinogens by the International Agency for Research on Cancer [IARC]), and this mode of use can be especially damaging because the packets are often in contact with oral mucosa for long durations.[13]

- **Alcohol consumption.** Heavier consumption of alcohol is associated with increased HNC risk. There is also a possibility of genetic susceptibility to HNC among certain heavy drinkers of alcohol that may predispose them to such cancers.[7, 14] The high alcohol consumption that for some accompanies tobacco use might play a synergistic role in causing HNC as well.[15]
- **HPV infection.** Incidence of HPV-related HNCs, specifically HPV-positive oropharyngeal cancer (OPC), has been growing quickly. HPV itself is widespread in the world's population, making it a common risk factor. OPC is the most common HPV-positive cancer, with distinctly different demographics from non-HPV-associated OPC. Individuals with HPV-positive HNCs tend to be younger, healthier (fewer comorbid diseases than in long-term tobacco and alcohol users), and have different behavior-related risk factors, including more sexual partners and earlier ages of onset of sexual activity.

  Currently there are more than 100 viral types of HPV. HPV 16 is considered to be responsible for the majority of HPV-associated cancers. There is evidence that vaccination against HPV 16 and 18 could prevent 90% of oral HPV infections within four years, but no data yet show if vaccination could translate into lower rates of OPC.[3]

  Some sources conflate HPV-positive oral cancer with HPV-positive oropharyngeal cancer. At this time there is a significant difference in prognosis between HPV-positive and HPV-negative OPC. This is not the case for HPV-positive and HPV-negative oral cancers. The role of HPV in these cancers is not yet fully understood.[16]
- **Other viruses**
  - The Epstein-Barr virus, a type of herpes virus ubiquitous in all human populations, is classified as a Group I carcinogen by the IARC due to its association with certain lymphoid and epithelial malignancies. It is also implicated as an etiologic agent in nasopharyngeal cancer.[7, 17]
  - The Hepatitis C virus may be associated with non-oropharyngeal cancers and with HPV-positive OPC. This is a recent finding which is still being confirmed.[7, 18]
  - Those with human immunodeficiency virus (HIV) are at increased risk of malignancy generally and for OPC specifically, with a two- to three-fold increased risk of head and neck SCC.[7] This is likely associated with this population's higher rates of concomitant HPV infection.[19]



HNC Staging Updates

HNC is staged using the tumor, node, metastasis (TNM) system. On January 1, 2018, the AJCC Cancer Staging Manual, Eighth Edition (AJCC 8) went into clinical effect[1] and brought several important staging changes for HNC. The three most significant are:[16] depth of invasion (DOI) in oral cancer was added to the T classification for oral cavity cancers; existence of extranodal extension (ENE) was added as a staging factor to the N category except for nasopharyngeal cancer and HPV-positive OPC; and a new and separate staging system was introduced for high-risk HPV-positive OPC.

- DOI was added to the T category for HNCs as a better measure of tumor aggressiveness than overall tumor size, replacing tumor thickness. DOI is measured "from the horizontal line of the basement membrane of the adjacent healthy squamous mucosa until the deepest portion of tumor invasion."[20] Data over several decades have shown that DOI is a negative prognosticator in cancers of the tongue, buccal mucosa, and floor of the mouth.[16] Replacing tumor thickness with DOI in the T classification is expected to yield better hazard discrimination.[20]
- ENE was added to the N category as a factor in the clinical and pathological staging of HNCs in all anatomic sites, with the exception of HPV-positive OPC. Pathologic ENE is defined as extension of a metastatic carcinoma through the fibrous capsule of a lymph node. ENE is subdivided into microscopic (ENEmi), which extends 2 mm or less from the nodal capsule, and macroscopic (ENEma), which extends more than 2 mm or can be detected without a microscope. Clinical ENE is based on unambiguous clinical evidence, not only radiographic, of gross ENE.[16]
- Staging criteria for OPC was the most significant category of changes. Staging criteria are now in two separate lists and are based on HPV status (positive or negative). HPV status is to be determined using immunohistochemistry (IHC), a technique for detection of protein markers that can aid in tumor classification and diagnosis of several cancers. In this case, IHC is used to detect p16, a tumor suppressor protein that overexpresses in the presence of transcriptionally active HPV. It has been found to be a good surrogate marker for the older polymerase chain reaction (PCR) test.[21] Testing for p16 is more accessible, yields easy to interpret results, and costs significantly less to administer than PCR. The College of American Pathologists recommends that p16 IHC be reported as positive when there is "at least 70% nuclear and cytoplasmic expression with at least moderate to strong intensity."[36] Tumors that test negative for HPV are staged using Table 1, and those that test positive are staged using Table 2.[1]

Table 1. Oropharyngeal Cancer (p16 negative)	
T	**Primary Tumor**
Tis	Carcinoma in situ
T1	Tumor ≤2 cm in greatest dimension
T2	Tumor >2 cm but not >4 cm in greatest dimension
T3	Tumor >4 cm in greatest dimension or extension to lingual surface to epiglottis
T4	Moderately advanced or very advanced disease
T4a	Moderately advanced local disease: Tumor has invaded the larynx, extrinsic muscle of tongue, medial pterygoid, and hard palate or mandible
T4b	Very advanced local disease: Tumor has invaded the lateral pterygoid muscle, pterygoid plates, and lateral nasopharynx or skull base or encases carotid artery
N	**Regional Lymph Nodes (Pathological, pN)**
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, ≤3 cm in greatest dimension and ENE(-)
N2	Metastasis in a single ipsilateral lymph node, ≤3 cm in greatest dimension and ENE(+); or >3 cm but not larger than 6 cm in greatest dimension and ENE(-); or metastases in multiple ipsilateral lymph nodes, none >6 cm in greatest dimension and ENE(-); or metastases in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension and ENE(-)
N2a	Metastasis in a single ipsilateral or contralateral node ≤3 cm in greatest dimension and ENE(+); or a single ipsilateral node >3 cm but not >6 cm in greatest dimension and ENE(-)
N2b	Metastasis in multiple ipsilateral nodes, none >6 cm in greatest dimension and ENE(-)
N2c	Metastasis in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension and ENE(-)
N3	Metastasis in a lymph node >6 cm in greatest dimension and ENE(-); or metastasis in a single ipsilateral node >3 cm in greatest dimension and ENE(+); or multiple ipsilateral, contralateral or bilateral nodes, any with ENE(+)
N3a	Metastasis in a lymph node >6 cm in greatest dimension and ENE(-)
N3b	Metastasis in a single ipsilateral node >3 cm in greatest dimension and ENE(+); or multiple ipsilateral, contralateral or bilateral nodes, any with ENE(+)
M	**Distant Metastasis**
M0	No distant metastasis
M1	Distant metastasis

Source: AJCC 8

Table 2: HPV-Mediated Oropharyngeal Cancer (p16 positive)	
T	**Primary Tumor**
T0	No primary identified
T1	Tumor ≤2 cm in greatest dimension
T2	Tumor >2 cm but not larger than 4 cm in greatest dimension
T3	Tumor >4 cm in greatest dimension or extension to lingual surface of epiglottis
T4	Moderately advanced local disease: Tumor has invaded the larynx, extrinsic muscle of tongue, medial pterygoid, and hard palate or mandible or beyond
N	**Regional Lymph Nodes (Pathological, pN)**
pN0	No regional lymph node metastasis
pN1	Metastasis in ≤4 lymph nodes
pN2	Metastasis in >4 lymph nodes
M	**Distant Metastasis**
M0	No distant metastasis
M1	Distant metastasis

Source: AJCC 8

Treatment

Current treatment recommendations for HNC call for a multidisciplinary approach, with the best outcomes for complex cases seen at high-volume treatment centers where expertise is concentrated.[23]

- Local disease (Stage I and II): 30% to 40% of patients will be diagnosed with local disease and can generally be cured with surgery and/or definitive (i.e., curative) radiation therapy (RT), which includes external beam RT and brachytherapy. Treatment often depends on accessibility of the anatomic site for surgery and associated patient morbidity.[2] People with smoking and alcohol-related HNC, for example, are at risk for recurrence and second primary tumor occurrence, so alcohol and smoking cessation are important, as is close surveillance during follow-up. Surgical approaches may include: wide local excision for easily accessible sites; minimally invasive techniques such as transoral laser microsurgery (TOLM) for cancers of the larynx and hypopharynx; and transoral robotic surgery (TORS) for cancers of the oropharynx.[23] The current standard of care requires intensity-modulated radiation therapy (IMRT) and image-guided radiation therapy (IGRT).[23]
- Locally advanced disease (Stage III and IV): More than 60% of HNC patients are diagnosed with locally advanced disease, which carries a high risk of recurrence, distant metastases, and has poor prognosis. Treatment often includes a combination of surgery, radiotherapy, and chemotherapy.[2] The oral cavity is usually accessible for surgery as a primary treatment. Because oral cavity tumors are generally aggressive, postoperative RT often combined with chemotherapy is common. For cancers of the pharynx and larynx consideration of preserving function is important, so TORS, TOLM, and chemoradiotherapy are often used. For cancers of the nasopharynx, RT is the primary treatment for locoregional disease as this area is not anatomically accessible for surgery. The addition of chemotherapy in more advanced-stage disease can improve the likelihood of survival. Salivary gland cancers are primarily treated with surgical resection for lower-grade tumors and additional RT for higher-grade carcinomas.[23]

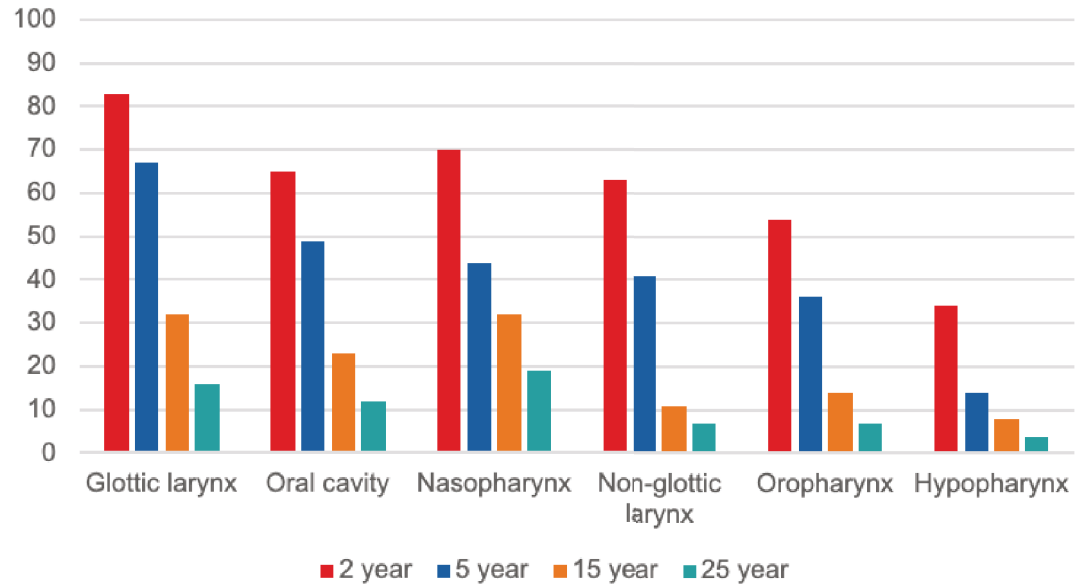
- HPV-positive OPC. This is currently being treated the same as HPV-negative OPC. Clinical trials are being conducted to look at deintensification of treatment for these patients.[23]
- Recurrent and/or metastatic disease. This develops in about 65% of patients. Several clinical trials have shown a survival benefit of adding immune modulators to standard therapy.[2]

Survival Outcomes

The longest-running cohort study of HNC patients was a 2014 study which followed 1,657 individuals from British Columbia, diagnosed with SCC of the oral cavity, pharynx, or larynx, between 1986 and 1990, for up to 25 years. Overall survival (OS) was tracked and compared by cancer site (using AJCC 5 staging), treatment received, and risk factors. Overall survival at 5, 15, and 25 years for all sites in the aggregate was 64%, 46%, and 21%, respectively. Median age at diagnosis was 63 years, 74% of individuals were male, and 43% were diagnosed at stage III or IVA. Median overall survival length ranged from 1.4 to 8.7 years, with glottic larynx cancer having the longest and hypopharynx cancer the shortest.

Figure 1 shows percent OS at 2, 5, 15, and 25 years by anatomic site. Risk factors associated with poorer survival included: older age, male gender, later stage at diagnosis, and oropharyngeal or hypopharyngeal disease.[24]

Figure 1. Overall Survival (%) of SCC HNC by site in Canadian Patients Diagnosed 1986-1990



Source: Tiwana MS, et al. 25-Year Survival Outcomes for SCCs of the Head and Neck. Oral Oncology 2014[24]

In a U.S. cohort from the Carolina Head and Neck Cancer Study,[25] 10-year survival rates of patients with SCC of the head and neck were examined in patients who had survived five years. Patients with HNC (SCC) were compared to age-matched non-cancer controls, stratified by p16 status and smoking status. OS at 10 years was 87% for p16+ oropharynx, 56% for p16- oropharynx, 69% for oral cavity, 67% for larynx, and 51% for hypopharynx. Predictors of mortality included initial stage at diagnosis, anatomic site, smoking status, and p16 status, with p16+ individuals having more favorable prognoses.[25]

Survival for this cohort likely looks more favorable when compared to other studies because patients were selected who had already survived for five years and were followed for an additional five years, as opposed to following from time of diagnosis. For an estimate of five-year survival of U.S. individuals followed from time of diagnosis, see the SEER data in Table 3.[26]

Table 3: Five-Year Survival Rates for HNC by Site and Stage at Diagnosis (SEER 2009-2015)			
Cancer Site	**Five-year Survival (Localized)**	**Five-year Survival (Regional)**	**Five-Year Survival (Distant)**
Salivary glands	94%	65%	35%
Nasopharynx	82%	73%	48%
Oral cavity and oropharynx			
Lip	92%	60%	28%
Tongue	81%	68%	39%
Floor of mouth	77%	38%	20%
Nasal cavity and paranasal sinuses	84%	51%	42%
Larynx and hypopharynx			
Supraglottis	61%	47%	30%
Glottis	83%	48%	42%
Subglottis	60%	33%	45%
Hypopharynx	59%	33%	21%

Source: Cancer.org[26]

Several other long-term cohort studies conducted in different global populations had similar results. In a 10-year study of prognostic factors for HNC survival in an Italian cohort (n=482), patients with primary SCC of the head and neck diagnosed in 2002-2012 were followed for up to 10 years post-diagnosis with median follow-up of 49 months. Five-year overall survival, combined across HNC sites, was 60.6%. By site, OS was 49.0% for oral cavity; 54.8% for oropharynx; 50.0% for hypopharynx; and 63.4% for larynx. Predictors of mortality included older age and more advanced tumor stage at diagnosis. Drinking eight to 14 alcoholic beverages per week was also a predictor of recurrence, and later stage at diagnosis and smoking for more than 40 years were predictors of a second primary HNC.[27]

In another study from Italy,[28] five-year overall survival of HNC was calculated for 801 patients from five centers and predictors for overall survival evaluated. OS at five years was 64% for all HNC sites in aggregate, and survival by site was 55% for oral cavity, 53% for oropharynx, 41% for hypopharynx, and 71% for larynx. Predictors of poor survival were older age, higher tumor stage, high alcohol consumption, and for oral cavity cancer, combined therapy was associated with poorer prognosis. Higher tumor stage at diagnosis was also a predictor of recurrence and duration of smoking a predictor of second primary cancer.

Finally, a study examined a 1,829-patient cohort from the Scottish Audit of Head and Neck Cancer that were assessed 12 years after diagnosis. Overall survival was 26.3% across HNC sites and net survival was 41.4%. Predictors of mortality were anatomical site, age, cancer stage, treatment modality, World Health Organization (WHO) performance status, alcohol consumption, and smoking behavior.[29]

Additional Considerations

A separate discussion of several types of HNC is warranted, given differing predictors or prognoses. HPV-positive OPC has a better prognosis than HPV-negative OPC.[30] HPV-positive OPC is now understood to be an entirely different entity than traditional smoking/tobacco and alcohol-related OPC.[31] In a study that looked at a U.S. cohort of 4,454 OPC patients where overall survival for HPV-positive and HPV-negative individuals was calculated separately using AJCC 7 staging, overall survival at four years for stages I to IV was 61.8%, 56.3%, 61.1%, and 55.8%, respectively, for HPV-negative OPC, and 90.1%, 86.1%, 87.0%, and 80.1%, respectively, for HPV-positive OPC. Significantly more favorable survival was demonstrated for HPV-positive OPC.[32]

The ICON-S study[33] included 1,907 HPV-positive and 696 HPV-negative patients from seven centers in Europe and North America with a diagnosis of non-metastatic oropharyngeal cancer. It compared overall five-year survival for these patients using AJCC 7 staging and found that the staging performed poorly for HPV-positive patient stage separation. Using recursive partitioning analysis (a statistical method for multivariable analysis) and adjusted hazard ratio modeling, the study derived and tested new stage classifications for HPV-positive OPC. These new classifications were found to be a more valid way to stratify patients into stages and were incorporated into AJCC 8. Indeed, in the new classification system, 48% of HPV-positive stage III and IV cancers under AJCC 7 staging criteria would be stage I using AJCC 8 staging.[16]

Available data on survival outcomes for HNCs at salivary gland sites is limited due to that cancer's rarity. Predictors of survival are also different for this cancer than for other HNCs. A 20-year retrospective cohort study reviewed pathology data on 75 U.S. patients diagnosed with salivary duct carcinoma from 1995 to 2014.[34] Mean age at diagnosis was 66 years, 71% were male, and most primary tumors were in the parotid gland (83%), followed by the submandibular gland (12%). Histologically, 41% of the cancers were classified as carcinoma ex pleomorphic adenoma, 69% had perineural invasion, 58% showed extracapsular spread, 31% were ERBB2 gene positive, and 61% had vascular invasion. The median OS was 3.1 years. Features associated with poor survival included perineural invasion, vascular invasion, and extracapsular spread.[34]

Nasopharyngeal cancer (NPC) is rare in North America and Europe but more common in Asia. A cohort of 527 patients treated at a Chinese medical center between 2007 and 2011 with confirmed NPC without metastases was followed for up to five years. The median age of the cohort was 44 years, 75% were male, and 99% had non-keratinizing carcinoma. The findings included that five-year overall survival was 80.9%, and significant prognostic factors associated with poor survival included older age and higher stage.[35]

Conclusion

Head and neck cancers represent a diverse spectrum of tumors. Risk factors include tobacco use, excessive alcohol consumption, and infection with certain viruses such as HPV. In general, prognosis depends on age, gender, stage, and anatomic location of the tumor, among other factors. The risk of recurrence or a new primary tumor can be of concern under certain circumstances.

HPV-positive OPC is now understood to be an entirely different entity than the traditional tobacco and alcohol-related OPCs, with a prognosis better than for HPV-negative OPC. As it is staged so differently in AJCC 8 from before, it is important for underwriters and medical directors to understand that HPV status now drives the criteria by which this cancer is staged as well as the overall prognosis. A pathology report for OPC without an HPV status noted will likely be difficult to categorize, but this should be an unusual occurrence as HPV testing is now recommended for all patients with newly diagnosed oropharyngeal squamous cell carcinoma.[36]

The other important takeaway for underwriters is to appreciate how vast is the field of head and neck cancer, in terms of the complex anatomical areas involved. Different anatomical areas may be closely situated but can have very different cancers with different prognoses. Ensuring an HNC is correctly categorized and staged is of the utmost importance. RF

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THE RISE OF HEMATOPOIETIC STEM CELL TRANSPLANTATION

Abstract

Hematopoietic stem cell transplantation (HSCT) is a life-saving procedure which is today the standard of care for many hematological malignancies. In recent years its purview has expanded: the procedure has found new utility in the treatment of immunological and hereditary conditions; and other novel areas are being explored as well. Because of this broadening scope of applicability and several recent procedural improvements, insurers need to understand HSCT today. This article provides an overview.

What is HSCT?

Hematopoietic stem cell transplantation (HSCT), also known as bone marrow transplantation, is the procedure wherein hematopoietic stem cells (HSC) – that is, blood-forming stem cells – are transplanted with the intention of repopulating the recipient's bone marrow with new, healthy cells. The donor can be the actual patient, a relative, or even an unrelated individual.

The first human allogeneic bone marrow transplant – transplantation from an outside donor – was performed in 1957 by physician and cancer researcher Dr. E. Donnall Thomas, who is also known as the father of bone marrow transplantation. Initial results were disappointing, with very high mortality due to graft failure, graft vs. host disease (GVHD), and primary disease relapse.

The procedure did, however, establish that bone marrow infusion could lead to hematological reconstitution in patients with acute leukemia.[1] Major progress came in the late 1960s with the discovery of the human leukocyte antigen (HLA) system by immunologists Dr. Jean Dausset, Dr. Johannes Joseph Van Rood, and Rose O. Payne, Ph.D. The HLA is what enables the human immune system to distinguish its own proteins from those of foreign entities.[2, 3] Its discovery permitted unrelated donors to be typed and matched to recipients, which increased the success rate of these transplants. In 1980, Dr. Dausset received the Nobel Prize in Physiology or Medicine, together with Baruj Benacerraf and George Davis Snell, for their discoveries of "genetically determined structures on the cell surface that regulate immunological reactions." Dr. Dausset was recognized for his identification of human leukocyte antigens and the genes that code for them. In 1990, Dr. Thomas received a Nobel Prize in Physiology or Medicine as well for his work in cell transplantation.

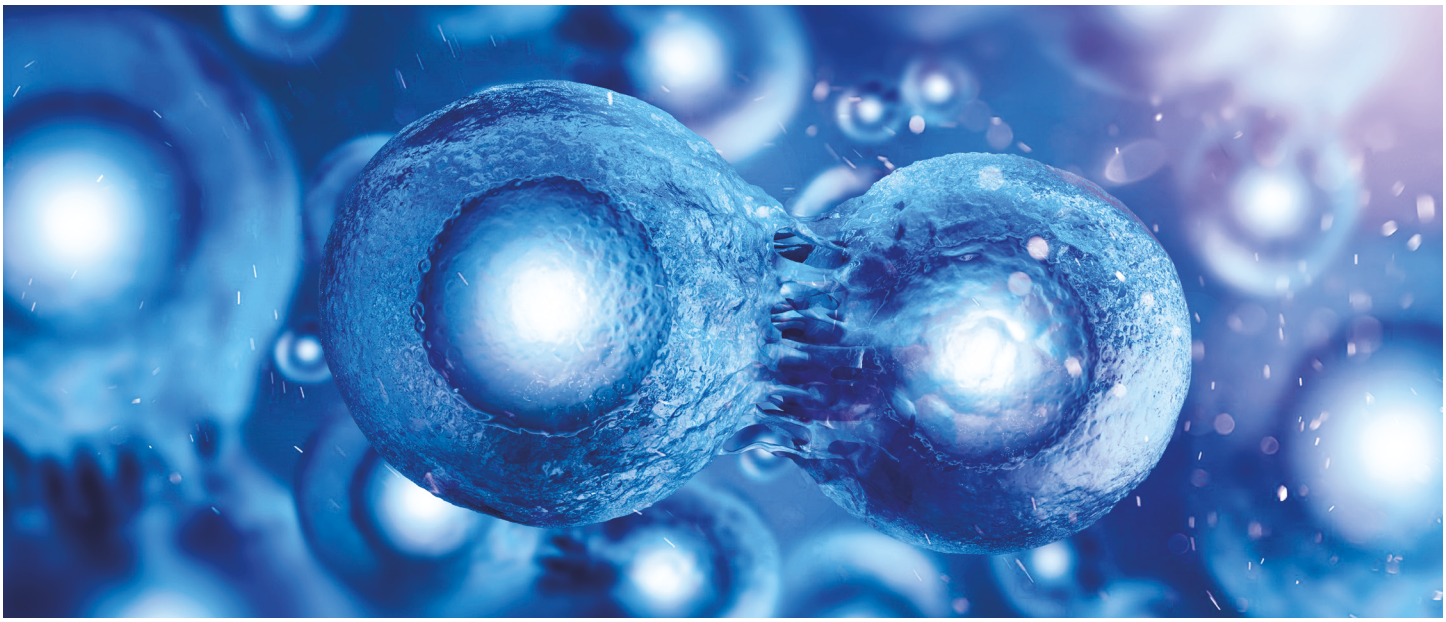
Today, HSCT is standard of care for many hematological malignancies, and hematopoietic stem cells are the most routinely transplanted type of adult stem cell. More than one million HSCTs have reportedly been performed worldwide during the past six decades; this number is steadily rising,[6] and survival rates are improving.

ABOUT THE AUTHOR

Dr. Sheetal Salgaonkar, DBIM
ssalgaonkar@rgare.com

Dr. Sheetal Salgaonkar, DBIM, is Vice President and Medical Director with RGA and a member of RGA's Global Medical team. Based in Mumbai, India, she provides underwriting and claims consultation for the regional offices in the International division, and is involved in product development, medical underwriting training, and development of guidelines for RGA's Global Underwriting Manual.

Dr. Salgaonkar has been a part of the Federation of Indian Chambers of Commerce & Industry's Task Force for Critical Illness and a member of the subcommittee for Policy Formulation on Financial Inclusion of Persons with Disabilities for the Indian Insurance Industry. She is also treasurer of the Indian Insurance Medical Officer's Association (IMOK) and was the scientific chair for the International Committee for Insurance Medicine's 2019 meeting, held in Mumbai. She has significantly contributed to the course curriculum of the Underwriting Diploma and Advanced Underwriting Diploma, which is a joint initiative of Association of Insurance Underwriters (AIU) and Insurance Institute of India.



About Stem Cells

Stem cells are nonspecialized (or basic or generic) cells of multicellular organisms. All stem cells have two fundamental characteristics: the ability to duplicate precisely by cell division, known as self-renewal, so that the daughter cells are exactly the same as the parent cells; and differentiation, which refers to the ability of these cells to mature into a wide range of specialized cells.

There are three main types of stem cells:

- Totipotent, also called omnipotent, which are stem cells with the potential to become any cell of an organism, including the umbilical cord and placenta. The zygote is an example of a totipotent stem cell.
- Pluripotent, also known as embryonic stem cells, which can differentiate into every type of cell in an organism except the umbilical cord and placenta. These cells are descendants of totipotent cells.
- Multipotent, also known as adult stem cells or somatic stem cells, which are found throughout an organism after cell differentiation and development. Multipotent cells can differentiate into a number of cell types, but only those in closely related cell families. Hematopoietic, neural, and mesenchymal cells are types of multipotent stem cells.

Types of HSCTs

The two types of HSCT procedures utilized today are autologous, where the donor and the patient are the same, and allogeneic, where the donor is other than the patient.

The advantages of autologous transplantation include faster patient cell count recovery, less transplant-related morbidity, shorter hospital stays, and reduced cost compared with allogeneic grafts. Relapse of the underlying malignancy is the major risk.[5]

Allogeneic transplants consist of hematopoietic stem cells from an external donor. An advantage of an allogeneic graft is that the donor's immune system can contribute significantly to the elimination of cancer via graft vs. tumor (GVT) effect.[6] The risk of disease relapse is low, but the procedure is associated with graft vs. host disease (GVHD).

Indications

Indications for HSCT are constantly being expanded and refined, as research progresses and new efficacies are discovered (Table 1, below). The American Society for Blood and Marrow Transplantation (ASBMT) and the European Blood and Marrow Transplantation Group (EBMT) have published guidelines that classify the many conditions for which HSCT is an indicated treatment. The guidelines provide three categories of indications: standard of care, including clinical option; developmental; and not generally recommended.

The majority of HSCTs performed for lymphoid malignancies, are autologous, while most done for myeloid malignancies are allogeneic. Autologous HSCT is also preferred for patients with autoimmune disorders.[7, 8, 9]

Table 1: Indications for HSCT	
Category	**Indications**
Hematologic malignancies	**64% lymphoid malignancies** • Acute lymphocytic leukemia (ALL) • Chronic lymphocytic leukemia (CLL) • Hodgkin lymphoma (HL) • Non-Hodgkin lymphoma (NHL) • Plasma cell disorders (PCD), including multiple myeloma (MM) and others
	25% myeloid malignancies • Acute myeloid leukemia (AML) • Myelodysplastic or myelodysplastic/myeloproliferative neoplasm (MDS or MD/MPN overlap) • Myeloproliferative neoplasm (MPN) • Chronic myeloid leukemia (CML)
Solid tumors	**4% solid tumors** • Pediatric solid tumors • Soft tissue tumors • Breast cancer • Renal cancer
Nonmalignant disorders	**7% nonmalignant disorders** • Hemoglobinopathies (sickle cell disease, thalassemia) • Inherited metabolic disorders • Bone marrow failure • Primary immunodeficiencies • Autoimmune disorders (multiple sclerosis, systemic sclerosis)

HSCT For All – A Closer Reality

The availability of various sources of stem cells as well as alternative donor options have made it possible to offer HSCT as a treatment option for a wider group of patients.

Hematopoietic stem cells can come from three sources: harvested bone marrow, peripheral blood stem cells, and umbilical cord blood.[7]

Bone marrow cells are harvested from donors in a surgical procedure. They are extracted either from the hip bone (specifically, the posterior iliac crest) or from the sternum. Since the 1990s, scientists have been able to collect stem cells directly from peripheral blood. The procedure involves an injection of granulocyte colony stimulating factor (G-CSF), which causes marrow stem cells to migrate into circulating blood. Peripheral blood stem cells (PBSCs) can then be collected by apheresis, which is a much less invasive procedure than bone marrow collection. Over the past decade, PBSCs have become the preferable stem cell source for many transplant centers, accounting for around 75% of all HSCTs.[10]

PBSC patients benefit from faster engraftment, but the risk is higher rates of GVHD.[10] High-level evidence has shown that there is no difference in overall and disease-free survival between bone marrow and PBSC HSCTs.[11]

Umbilical cord blood (UCB) cells are an alternative source to bone marrow cells and PBSCs. These cells, as the name implies, are extracted from the umbilical cord after birth. UCB offers several advantages: easier availability, higher tolerable HLA disparity as the cells are naive, and lower risk of GVHD and relapse.

HLA Matching

The strongest determinant of outcomes for allogeneic HSCT is donor-recipient human leukocyte antigen (HLA) matching.[12] HLA matching identifies the HLA A, B, C (Class I) and DR, DQ, DP (Class II) loci present on donor and recipient cells. Each person has two types of A, B, C, and DR antigens, one inherited from each parent.

The best donor for an allogeneic HSCT is either an HLA-matched sibling or an unrelated donor who is a complete HLA match (8/8 or 10/10). Unfortunately, less than 30% of patients have a sibling who is a complete match.[13] If an adult-matched sibling or matched unrelated donor (MURD) cannot be identified, recent advances in HLA research have enabled three alternative donor options:

- **Mismatched unrelated donor (MMURD)**. This refers to an adult unrelated donor who is mismatched in at least one antigen or allele at HLA-A, B, C, or DR.
- **Haploidentical-related donor**. This would be a family member with only one of the two HLA haplotypes genetically identical with the patient. These are usually biological parents, children, or siblings.
- **Umbilical cord blood (UCB) stem cells**. UCB stem cells from unrelated donors are commonly used when a donor match is otherwise unavailable. Since these cells can be obtained rapidly from cord blood banks, they may be a better option when the patient need is urgent. The downside is that cord blood contains fewer hematopoietic stem cells than bone marrow or peripheral blood, so engraftment tends to be slower, the risk of graft failure is higher, and immune reconstitution can be slower, which may lead to infections.[14]

An exciting new development is the use of either autologous or unrelated UCB cells in therapies for diseases such as cerebral palsy, hypoxic ischemic encephalopathy, and dilated cardiomyopathy.[15]

The Procedure

HSCT generally requires four steps, depending on the source of the stem cells:

- **Cell collection.** HSCs are collected either by apheresis from peripheral blood or by bone marrow harvest. PBSCs are collected after stimulation either with growth factors alone or growth factors plus chemotherapy.
- **Processing and cryopreserving.** HSCs are then processed and cryopreserved until needed for transplant.
- **Preparation and conditioning.** These regimens aim to eradicate diseased cells, suppress the recipient's immune system, and create space for donor cells in the recipient's marrow. Traditionally, myeloablative regimens (MA), which used high doses of chemotherapy and total body irradiation (TBI), were used for preparation and conditioning. A major development over the past 15 years has been the development of reduced intensity conditioning (RIC) and nonmyeloablative (NMA) conditioning. These regimens keep treatment intensity just high enough to avoid graft rejection. The goal is to promote engraftment and let the GVT effect eliminate tumor cells. The reduction in morbidity and mortality in transplants where RIC and NMA regimens were used has made allogeneic HSCT available for patients age 60 and older – the age group with the highest prevalence of most hematopoietic malignancies.[16] (Table 2, below)
- **Stem cell infusion.** After conditioning, the stem cells are infused intravenously.

Table 2: Conditioning regimens – favorable and unfavorable factors

Myeloablative	Nonmyeloablative or Reduced Intensity
• Used in patients who are younger and with no comorbidities	• Can be used in older patients with comorbidities
• Dose-intensive chemotherapy +/- TBI	• Lower doses of chemotherapy + /- TBI
• Eradicates malignant disease	• Reduces conditioning-related toxicity
• Suppresses immune system to prevent graft rejection	• Relies mainly on GVT effect

Complications

Although outcomes of HSCT tend to be good and patients show considerable improvement over time, the procedure is associated with significant related morbidity, mortality, and long-term health issues.

Major complications include:

- **Infections** are the most important cause of morbidity and mortality during the post-transplant period of neutropenia. In the pre-engraftment period (0-30 days after transplantation) bacterial infections followed by fungal infections (e.g., *Candida*, *Aspergillus*) predominate due to low white blood cell counts and the disruption of normal barrier defenses.[17] The most important pathogens in the early post-engraftment period (30 to 100 days) are viruses such as cytomegalovirus (CMV) and other pathogens such as *Pneumocystis* and the previously mentioned *Aspergillus*. In later stages (>100 days post transplantation), the immune system recovers, reducing the risk of opportunistic infections. Chronic GVHD (discussed in the next section) and continued immunosuppression can lead to infection with viruses such as CMV, varicella zoster virus (VZV or shingles), and Epstein-Barr virus (EBV), as well as with encapsulated bacteria such as *Hemophilus influenzae* and *Streptococcus pneumoniae*.[18,19]

- **Graft vs. Host Disease (GVHD)**, which is the major complication of allogeneic HSCT, is an immunologically mediated reaction of donor cells (the graft) to host (or recipient) cells. GVHD develops in >50% of these patients despite prophylaxis and can be life-threatening.

  For GVHD prophylaxis, patients receive immunosuppressive drugs, most commonly a combination of cyclosporine and methotrexate or mycophenolic acid. In contrast to organ transplantation, GVHD prophylaxis can be tapered off and stopped in patients who do not develop GVHD after six to 12 months.[20]

  GVHD can be acute or chronic. Although GVHD has traditionally been classified as acute or chronic based on a cutoff of 100 days after transplantation, it is now widely recognized that there is extensive overlap in the time course at presentation. Each is a clinically distinct entity with very different pathophysiologic mechanisms.

  - **Acute GVHD** generally develops within the first four to five weeks after transplant. Its incidence and severity are directly related to the degree of HLA mismatch. It is an inflammatory reaction involving the skin, the liver, and the GI tract.[21]
  - **Chronic GVHD (cGVHD)** resembles an autoimmune disorder. Fibrosis and sclerosis of involved tissues are its characteristic features. In severely affected individuals it can involve multiple organ systems, including skin, musculoskeletal, gastrointestinal, lungs, GI, eyes, liver, and genitourinary systems. cGVHD is a major cause of long-term morbidity and mortality in survivors of HSCT and is the most significant determinant of post-transplant quality of life as well. Risk factors for cGVHD include older age, prior acute GVHD, donor type, and use of PBSCs.[22, 23]
- **Graft failure/rejection** is an uncommon but serious complication of HSCT. It is defined as either lack of initial engraftment of donor cells (primary graft failure) or loss of donor cells after initial engraftment (secondary graft failure). Risk factors include RIC/NMA regimens, UCB transplants, and HLA-mismatched transplants.[24]
- **Secondary malignancies** are a post-HSCT concern. The magnitude of risk of secondary malignancies shows a 4- to 11-fold relative risk (RR) in several studies and a cumulative incidence at 15 years of 10% to 12%.[25] Secondary malignancies are divided into three groups:
  - **Post-transplant lymphoproliferative disorders (PTLD)**, which are almost exclusively seen in allogeneic HCT recipients and comprise a heterogeneous group of lymphoid proliferations primarily involving B-lymphocytes, which result from EBV infection.
  - **Hematologic malignancies**, such as MDS and AML.
  - **Solid cancers**, with lifelong cancer screening recommended for all HCT survivors in accordance with established guidelines.

Post-Transplant Prognosis and Survival

HSCT outcomes are influenced by the patient's age, the nature and stage (if cancer) of the disease, and transplant-specific variables such as donor/recipient histocompatibility and the time interval from diagnosis to transplant.

Disease relapse is the main cause of treatment failure in the first two to four years after transplantation. Patients who do not relapse through this time period have relatively high rates of subsequent survival.

Cumulative chemotherapy and radiation exposures can injure normal tissues, leading to premature onset of chronic health conditions such as subsequent neoplasms, congestive heart failure, coronary artery disease, and endocrine and musculoskeletal abnormalities.

Pediatric HSCT survivors are more likely to experience psychological distress and low quality of life in adulthood compared with the general population.[26]

Long-term HSCT survivors need continued lifelong surveillance for screening, early detection, and timely treatment of late complications. Although studies vary in methodology and patient characteristics, together they indicate high probability of long-term survival in this patient population, although their life expectancy continues to lag that of age- and gender-matched peers from the general population for at least 15 to 20 years after HSCT.[27]

Applications of HSCT in Insurance

From an underwriting point of view, HSCT is a curative therapy for many malignant and nonmalignant hematological diseases. Although the primary disease is a major factor, individuals who have undergone HSCT still have long-term effects and might be offered life cover with a mild-to-moderate risk assessment a few years after a complication-free time interval has passed. HSCT survivors may have morbidity issues such as treatment-related chronic conditions as well as psychological distress and low quality of life. Therefore, offering living benefits may not be feasible.

HSCT is covered as a major payout in many critical illness products. Definitions vary, and a few points raise concern:

- Some policy definitions cover only HSCT recipients who have undergone MA conditioning regimes. With the increasing use of RIC/NMA regimens for the same primary disease, definitions need to be updated and priced accordingly, as such claims could arguably otherwise meet the definition.
- Most policy definition wordings exclude stem cell transplants, but as HSCT is a type of stem cell transplant, a rewording of the definition would be technically appropriate.
- Some products cover only allogeneic transplants, the view being that autologous HSCT uses a patient's own cells and so are not equivalent. However, as autologous and allogeneic transplants are performed for the same hematological indications, employ nearly identical procedures, and have the same potential complications, this view can be challenged.

Conclusion

HSCT is a curative treatment for many hematological malignancies as well as immunological and hereditary conditions. Over the years, several advances, such as new conditioning regimes (NMA and RIC) and alternative donor and cell source options, have made HSCT safer, leading to increasing numbers, expanding indications, and improved patient survival. In the coming years, HSCT is likely to become more common, efficient, and effective. RF

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CANDIDA AURIS: A QUIETLY EMERGING HEALTH THREAT

Abstract

Candida auris (C. auris) *is a recently emerged multi-drug resistant fungus. Its four main strains have adapted swiftly since the first was detected and identified in Japan more than a decade ago. At this point, it has spread around the world and is most problematic in high-dependency healthcare environments such as hospital intensive care units (ICUs) and nursing homes. Concerns about* C. auris *reflect rising worries about antimicrobial resistance (AMR), a worldwide health threat which researchers believe could potentially cause up to 10 million deaths per year by 2050.*[1, 3] *With one in five deaths worldwide already caused by sepsis (stemming in some cases from candidiasis),*[10] *this 10 million statistic cannot be ignored.*

The past several decades have seen microbes become increasingly resistant to the modern arsenal of antimicrobial drugs, due in large part to misuse and overuse of antibiotics in medicine and animal agriculture. The early 20th century saw great advances in understanding and controlling infectious disease, but research for more than a half-century has focused largely on understanding and treating cancer, cardiovascular conditions, autoimmune diseases (e.g., multiple sclerosis and rheumatoid arthritis), and chronic diseases such as type 2 diabetes. The problem is compounded by the fact that few new antimicrobial drugs have been discovered or developed in the last 25 years.[11]

This article will discuss the emerging Candida *strain of* C. auris *and its growing impact on healthcare and insurers.*

What is *Candida*, and What is *Candida auris*?

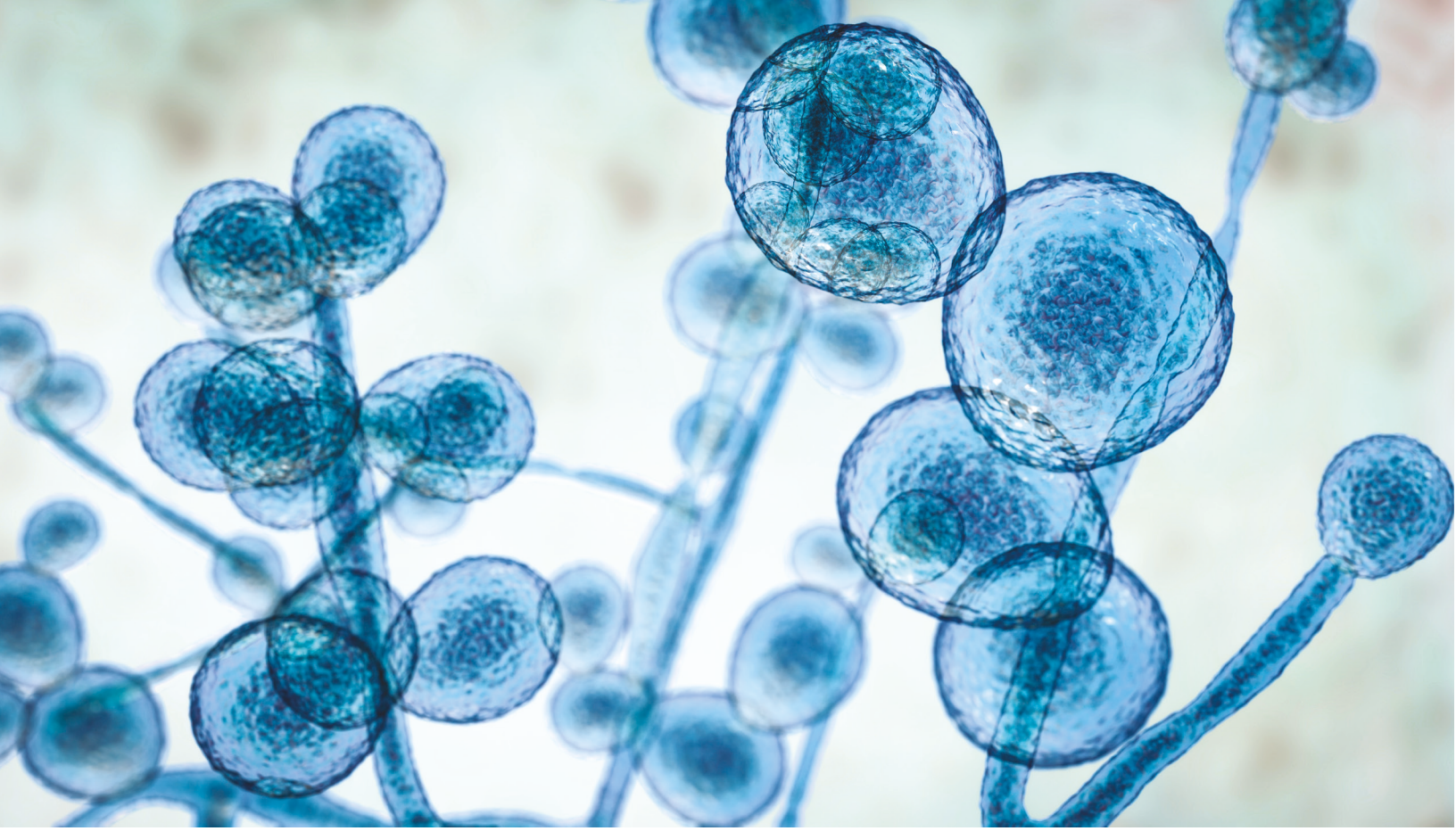
Candida is a well-known fungus with multiple strains, the majority of which live harmlessly on the skin and inside the human body and are kept in check by co-existing bacteria in the microbiome. Candidiasis, the fungal infections it causes, is most commonly seen in the mouth and throat, the gastrointestinal tract, the vagina, and in skin folds. (Yes, diaper/nappy rash is a form of candidiasis.)

Invasive candidiasis happens when *Candida* enters the bloodstream or internal organs, which can occur during surgeries and invasive procedures such as catheterization, intubation, and tracheostomies. Broad-spectrum antibiotics and overuse of antifungals, as well as the oral steroid medications that treat asthma and autoimmune conditions, can leave the body vulnerable to *Candida* infections. Corticosteroids weaken the immune system, allowing fungal infections to take hold. Diabetic individuals are also very susceptible to fungal infections due to altered functions of their immune systems, particularly in those with poor glycemic control, or as a direct effect of their elevated blood glucose levels, which encourages fungal colonization.

ABOUT THE AUTHOR

Sharon Latocha
slatocha@rgare.com

Sharon Latocha is a Senior Underwriting Consultant with RGA. Based in Australia, Sharon has over 30 years of underwriting experience. For the past seven years, she has provided RGA clients throughout Australia and New Zealand with her high-level technical underwriting expertise, presenting training seminars for new and experienced underwriters and contributing to underwriting, guideline development, and audits.



C. auris is a newer species of *Candida*. First identified and named in 2009, it causes bloodstream and intra-abdominal infection in surgical, intensive care, and other high-dependency healthcare situations, and is the first known species of *Candida* to be resistant to nearly every existing treatment. Indeed, some strains are already resistant to all currently available treatments, which in 2018 caused it to appear on the U.S. Centers for Disease Control and Prevention (CDC) list of urgent threats[4] as well as its list of nationally notifiable diseases (meaning that occurrences must, by law, be reported to government authorities).

Where Is It From, and Where Is It Now?

The manner of *C. auris'* evolution and how it behaves are most interesting. One of its unusual aspects is that its four known strains, or clades, appear to have emerged at approximately the same time in four widely-flung locations – east Asia, south Asia, southern Africa, and South America. Upon sequencing the genomes of *C. auris* taken from each location, it was found that the four clades have enough genetic similarities that they may have come from the same ancestor, but they are also genetically distinct from one another. This has led to a hypothesis that *C. auris* may have developed independently and simultaneously in multiple regions.[6]

Possible explanations offered as to how the separate clades emerged and evolved range from overuse of anti-fungal preparations in humans and livestock to climate change.[8,13] Despite the common assumption that fungi like warm, moist areas, few fungi can live, let alone grow, at the human internal body temperature of 37 degrees Celsius (98.6 degrees Fahrenheit), but *C. auris* has been shown to be able to live in temperatures as high as 42 degrees Celsius (107.6 degrees Fahrenheit).[8]

As little is currently known about *C. auris'* initial genesis it is hard to say if climate change may have played a part, but it is an interesting hypothesis. Indeed, if the climate change hypothesis is valid, *C. auris* may be the first human pathogen to have taken advantage of it, evolving from an environmental fungus into one infectious to humans.[9,13] Experiments have shown that certain fungi can readily adapt to growth at higher temperatures, and that fungal species in cities may be more thermotolerant than their rural counterparts. As *C. auris* is found on cooler human body locations, such as the skin and the ear canal, but not in the warmer gut, a theory put forth in 2019 posits that this fungus may have first adapted to warmer temperatures due to climate change. Its evolution into a human pathogen may have occurred by

first becoming infectious to an animal host before mutating into human infectivity. It is interesting to note that the first human *C. auris* infection was found in the human ear, an area cooler than core body temperature.[13] As the gap between internal human body temperature and ambient environmental temperature continues to narrow, new invasive fungal pathogens may also emerge.[13] Further research will be needed to understand *C. auris'* evolution.

As for spread, single and multiple incidence of *C. auris* cases have been reported in more than 30 countries (see Figure 1). At the end of 2019, the U.S. alone had nearly 1,000 confirmed cases in 16 states, the majority of which were in New York, New Jersey, and Illinois. Some of these cases were found in individuals who had recently spent time in healthcare facilities in India, Kenya, Kuwait, Pakistan, South Africa, the United Arab Emirates, and Venezuela.[12]

Figure 1: Map of *Candida auris* cases worldwide (areas of spread in red)

Why the Interest Now?

Since 2009, *C. auris* has been spreading quickly around the world. The infections it causes are difficult to diagnose using routine fungal cultures and require more sophisticated molecular diagnostic methods. The infections can also be severe, affecting the bloodstream, surgical wounds, and not surprisingly, ears. It is known to have caused cases of endocarditis, osteomyelitis, and endophthalmitis.[2]

Symptoms of *C. auris* infection include fever and chills, sepsis, little to no patient improvement while on antifungal therapy, coma, and organ failure.

Total mortality from it is also high, with CDC estimates ranging from 30% to as high as 60%. However, many of those cases were among individuals who were already ill and in high-dependency healthcare facilities. It is not known yet if the mortality rate is any worse than other invasive *Candida* infections but what is different is that *C. auris* is causing outbreaks in healthcare settings to an extent not previously seen with fungi.

The biggest risk with *C. auris* is that it is resistant to treatment. In the U.S. alone, 90% of *C. auris* strains are already resistant to fluconazole, more than 40% are resistant to amphotericin B, approximately 2% are resistant to echinocandins,[2] and a few *C. auris* strains are also known to be resistant to all three. Echinocandins are now the first line of defense against *C. auris*, but the few cases of its pan-resistance have occurred with people taking echinocandins, revealing a worrisome ability of *C. auris* to adapt quickly.

Transmissibility and Durability

Most invasive *Candida* infections are translocated from a patient's own skin or abdominal tract. Unlike bacterial infections, most fungal infections, including most species of *Candida*, are rarely transmitted from patient to patient in healthcare settings, so it is not usually subject to routine infection control measures.[2]

C. auris, however, behaves differently. It is easily transmitted among patients in healthcare facilities and has the ability to both contaminate and persist in the environment and on surfaces. In one ICU outbreak in the U.K., reusable axillary temperature probes (skin surface thermometers) were found to be most likely responsible.[2]

C. auris is also more durable than other fungi: it is salt-resistant and able to survive on wet or dry surfaces and non-biotic surfaces for long periods of time.[9] Specific anti-fungal agents must be used to decontaminate surfaces. From an infection control perspective, *C. auris* acts more like a multidrug-resistant, healthcare-associated bacteria than like a typical yeast.[2] An outbreak of 50 cases in a London cardiothoracic center found persistent presence of *C. auris* around the bed-space areas. In the first group of identified U.S. cases, not only did *C. auris* colonies remain on the skin and other body sites weeks to months after their initial infection,[7] the mattress, bedside table, bed rail, chair, and windowsill of the rooms where infected people had been placed were also found to still be contaminated one month after the infectious individuals had vacated.[7]

Who Is At Risk?

Individuals in good health are generally not susceptible to *C. auris*. More susceptible individuals tend to have: depleted immune systems; recently undergone surgery; open post-surgical wounds; lines/tubes or a tracheostomy; one or more chronic illnesses, such as diabetes; and/or taken broad-spectrum antibiotics or antifungal agents. At risk as well are individuals who have recently spent time in nursing homes, rehabilitation facilities, or other high-dependency care facilities where infected individuals were present.

Unfortunately, once a patient has been colonized with *C. auris*, the infection is very difficult to eradicate. This means infected people can spread it easily to other healthcare environments upon subsequent admissions. In addition, if they need more surgeries, they can develop serious complications.

Insurance Implications

It is unlikely a new life insurance applicant would have an active *C. auris* infection. However, insurers need to be alert to individuals who have had a recent surgery, had a recent extended stay in an overseas facility in a country where cases are endemic, or have a chronic health condition such as diabetes. Applicants may not have active infections but may still be colonized: some *C. auris* cases, according to the CDC, have gone undetected up to two years after hospitalization.

Current health status and any risk factors for persisting or re-emerging infective symptoms would need evaluating.

Caution should be applied in terms of disability cover, long-term healthcare and hospitalization products. Although those most at risk are already significantly unwell, some markets have a higher tolerance for sub-standard lives and there are some limited underwriting products with pre-existing conditions clauses. Since the risk factors can be vast, these clauses might not be entirely protective. In cases with recurrent or chronic *Candida* infections, further information and details may be required to fully assess the case.

On the claims side, given the high mortality rate of this microbe, especially from sepsis, death claims as well as health claims would need to be considered. There are implications for hospitalization and long-term healthcare covers that were purchased before chronic illness set in. A patient admitted for a scheduled standard surgical procedure may end up with an extended admission to the ICU that would cost much more than the original procedure.

Conclusion

C. auris is a new breed of pathogenic fungus. It is difficult to diagnose, treat, and eradicate. Its presence in healthcare facilities worldwide, especially nursing care, high-dependency care, and ICUs, is growing. More research is going to be needed to understand how this particular microbe is evolving and how best to deal with the global problem of antimicrobial-resistant pathogens, and this pathogen in particular. ReF

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Longer Life Foundation

An RGA/Washington University Collaboration

LLF INTERVIEW: COVID-19 RESEARCH

***Jeffrey P. Henderson, M.D., Ph.D. of Washington University School of Medicine in St. Louis and a former Longer Life Foundation (LLF) grant recipient, is one of the scientists at the forefront of research into using convalescent plasma (CP), i.e., plasma from those who have recovered from COVID-19, to help those with active disease. He recently provided deeper insight and perspectives on the subject and his work in an interview with* ReFlections.**

How did you become involved in this innovative line of COVID-19 research?

The effort began when Arturo Casadevall, M.D., Ph.D. at Johns Hopkins' Bloomberg School of Public Health, approached Michael J. Joyner, M.D., who is with the Mayo Clinic, and me about the possibility of collecting convalescent plasma (CP) on a national scale from patients who have recovered from COVID-19, and then using it to develop possible treatments.

Will you use plasma or serum in your research?

There is a rich history here. At the dawn of the twentieth century, it was found that the yellow liquid remaining after blood clots – serum – could be used to treat and prevent certain infections. It was later appreciated that serum contains antibodies. We can now harvest antibodies by removing cells from blood and keeping the liquid – plasma – that remains. We plan to use plasma because it is better tolerated by patients than serum and can be collected in greater volume.

Presumably, infected individuals produce multiple antibodies against SARS-CoV-2. Do we know if any or all of these might be protective (prevention/prophylaxis) as well as therapeutic?

A clear therapeutic effect from CP would be strong evidence favoring a role for antibodies in controlling clinical SARS-CoV-2 infections. The immune system generates numerous antibodies recognizing numerous antigens following infection by a viral pathogen like SARS-CoV-2. Any two antibodies may recognize different viral proteins or different parts of the same protein. Some, but not all, of these antibodies are able to prevent SARS-CoV-2 from infecting cells in culture. We will look with interest to see which, and how many, of these antibodies can prevent or treat infections in animal models of disease. Antibodies may also do other helpful things that aren't evident from experimental cultures. We will be open to finding these surprise interactions if they are present.

Will your trial focus on using CP in only severely/critically ill patients? If so, given the heterogeneity of the patient population as well as the significant other complications which can occur, will it be difficult to control for confounders?

Right now, CP is not being used in a controlled trial, and the decision to transfuse it is at the discretion of treating physicians, with patient approval. We are all still learning about the pathophysiology of the disease. There is likely a point in the development of COVID-19 where the tissue damage already done by the virus plays a larger role in the patient's status than the virus alone. In these situations, the possible antiviral effects of CP may be insufficient to significantly alter the disease's course.

Does CP therapy have the potential to be a game changer, or is it more likely to only marginally improve the relative risk of death for COVID-19 patients?

Following the limited experience of CP for SARS, which is caused by a coronavirus related to the COVID-19 agent, it seems likely that its greatest impact may be in early disease. A Lazarus-like effect in the severely ill is unlikely. We will watch with great interest as clinical experience with CP accrues.

Is there research looking at preventative uses of plasma or derived gamma globulin (or pooled hyperimmune globulin) in healthcare workers, the elderly, or those with a significant comorbid burden?

There is certainly interest and activity in many quarters on this; specifically, the use of a purified standardized gamma globulin preparation as well as of monoclonal antibodies with similar properties. The ability to deliver a more standardized dose, to concentrate the product, and to produce it in large quantities would certainly facilitate use for passive immunization of high-risk individuals until a vaccine can be developed. This kind of product, however, will require a longer development and approval time. CP, if effective, may fill that developmental gap until a purified product becomes available.

Could this research help inform those working on vaccines? Will knowing which antibody components are the most protective or therapeutic drive certain vaccine strategies? Or does your approach simply utilize whole, unprocessed plasma without identification of specific antibodies?

Our current approach utilizes whole plasma, which is FDA-approved. We qualify donors based on the existence of a minimal level of antibodies to the antigenically distinctive SARS-CoV-2 spike protein. With additional characterization of plasma, and possibly correlation with clinical outcomes, we hope to discern viral antigens that will stimulate an optimal protective immune response in a future vaccine.

How is your current research related to your past urinary tract infection (UTI) research which was funded by the Longer Life Foundation?

In both cases, preventing severe disease in high-risk patients has been a major focus. My LLF project sought to identify correlates of UTI susceptibility in elderly patients, with a focus on identifying and preventing septicemic progression. The particular focus on preventing progression to serious disease in that project mirrors the likely therapeutic niche for CP in COVID-19.

LLF SPOTLIGHT: COVID-19 RESEARCH

Dr. Jacco Boon, a Washington University School of Medicine in St. Louis infectious disease researcher and past LLF grant recipient (2015-2016), is also focusing on COVID-19. His lab has already switched from studying influenza and Bourbon virus to studying COVID-19. "We are trying to develop and optimize the mouse model for this virus and identify host genetic polymorphisms that associate with severe disease," he told *ReFlections*. His lab is also working on developing a hamster model, as it has shown promise in early studies with COVID-19. Finally, his lab is working on generating a live attenuated virus vaccine, using a molecular clone of the SARS-CoV-2 virus, in order to study its basic properties, including protein function (using deletion mutants) and test resistance mutations.

ReCite

Interesting and relevant articles to the field of insurance medicine recently appearing in the literature...

Relationship Between Poor Olfaction and Mortality Among Community-Dwelling Older Adults

Liu B, et al.
Annals of Internal Medicine. 2019 Apr 29; 170(10): 673-81.
https://europepmc.org/article/med/31035288

For humans, olfaction – the sense of smell – decreases gradually with age. Olfactory impairment affects up to 25% of older adults in the U.S., but unlike hearing or vision impairments, it often goes unrecognized. Poor olfaction has already been linked to higher mortality, but most studies have had a relatively short follow-up and have not explored potential explanations. Evidence is also now suggesting that olfactory impairment may be among the earliest symptoms of major neurodegenerative conditions such as Alzheimer's disease and Parkinson's disease.

This study examined olfaction in relation to all-cause mortality for two community-based groups of U.S. adults ages 71 to 82. It examined this aspect by sex, race, and general health status at 3, 5, 10, and 13 years follow-up, and investigated potential explanations through analyses of mediators and cause-specific deaths.

During follow-up, 1,211 of the 2,289 participants died by year 13. Compared with participants with good olfaction at baseline, those with poor olfaction had 46% higher cumulative risk for death at year 10 (mortality risk ratio 1.46) and 30% higher risk at year 13 (mortality risk ratio 1.30). Similar associations were found across gender and race.

The association was most evident among participants who reported excellent to good health at baseline (e.g., 10-year mortality risk ratio 1.62) but not among those who reported fair to poor health (10-year mortality risk ratio 1.06). In analyses of cause-specific mortality, poor olfaction was associated with higher mortality from neurodegenerative and cardiovascular diseases. Mediation analyses also showed that neurodegenerative diseases explained 22% and weight loss explained 6% of the higher 10-year mortality among participants with poor olfaction.

Editor's Note: *The increased mortality risk associated with poor olfaction, and the evidence suggesting it may be among the earliest symptoms of neurodegenerative diseases, may lead insurers to pay more attention to this condition when underwriting older lives in the future.*

Trends in Stroke Incidence Rates in Older US Adults: An Update from the Atherosclerosis Risk in Communities (ARIC) Cohort Study

Koton S, et al.
JAMA Neurol. 2020 Jan; 77(1): 109-13.
https://www.ncbi.nlm.nih.gov/pubmed/31566685

Validated stroke data in the Atherosclerosis Risk in Communities (ARIC) cohort study showed decreasing stroke incidence rates from 1987 to 2011 among people 65 years and older and no significant changes among younger ARIC participants. The study evaluated whether the decline in stroke incidence rates in older adults observed in prior studies continued in the subsequent six years, from 2011 to 2017.

At baseline, 55% of the 14,357 participants were women, and the mean age of all participants was 54.1 years (standard deviation 5.8 years). Overall, 1,028 incident strokes occurred among individuals 65 years of age and older. The rate of strokes for this group decreased 32% overall from 1987 to 2017, with decreases similar for men and women and across race. The decrease trend remained the same in the years 2011-2017 as it was for 1987-2011. No significant changes in rates were observed among those younger than 65 years.

Editor's Note: *These statistics are reassuring for the industry, especially in markets where critical illness benefits are offered for whole of life.*

Effects of acute sleep loss on diurnal plasma dynamics of CNS health biomarkers in young men

Benedict C, et al.
American Academy of Neurology. 2020 March 17; 94(11).
https://n.neurology.org/content/94/11/e1181

The importance of sleep for survival and cognitive performance has been recognized and studied for more than a century. However, only during the past decade has research begun to reveal the bidirectional relationship between sleep and long-term central nervous system health. A hallmark of the most common form of dementia, Alzheimer's disease, is the pathologic accumulation of both extracellular β-amyloid (Aβ) and intracellular tau proteins in amyloid plaques and neurofibrillary tangles, respectively. AD has been associated with poor subjective sleep as well as reduced sleep duration, quality, and efficiency, in what also appears to be a bidirectional relationship.

The study sought to assess the effect of acute sleep loss on the diurnal plasma rhythms of total tau (t-tau) and Aβ in healthy young men and to investigate biomarkers of neuroaxonal injury.

In a two-condition crossover study, 15 healthy young men participated in two standardized sedentary in-laboratory conditions in randomized order: normal sleep vs. overnight sleep loss. Plasma levels of t-tau, Aβ40, Aβ42, neurofilament light chain (NfL), and glial fibrillary acidic protein (GFAP) were assessed using ultrasensitive single molecule array assays or ELISAs, in the fasted state in the evening prior to, and in the morning after, each intervention.

Findings suggest that acute sleep loss results in an evening to morning increase in plasma levels of t-tau of 17.2% (compared to an increase of 1.8% with normal sleep), without concomitant changes in plasma levels of other biomarkers of AD, such as Aβ species, NfL, or GFAP. Whether the changes in t-tau in plasma in response to sleep loss reflect increased neuronal activity during sustained wakefulness, or alternatively, disrupted central or peripheral clearance, is unclear.

Editor's Note: *The use of data around sleep quality and sleep duration is becoming a hot topic in the insurance industry as an underwriting (and possibly even claims) instrument. Larger study cohorts may be warranted to determine the implications for recurrent long-term conditions (e.g., among shift workers), as well as interactions with other lifestyle and genetic factors.*

Major cardiac events for adult survivors of childhood cancer diagnosed between 1970 and 1999: Report from the Childhood Cancer Survivor Study cohort

Mulrooney DA, et al.
BMJ. 2020 Jan. 15; 368.
https://www.bmj.com/content/368/bmj.l6794

The aim of this study was to investigate the impact of modifications to cancer protocols, which minimize exposures to cardiotoxic treatments and preserve long-term health, on serious cardiac outcomes among adult survivors of childhood cancer.

The study involved 23,462 five-year cancer survivors who were under age 21 when treated for various cancers. The time period for treatment was from January 1, 1970 to December 31, 1999, and the cancers included leukemia, brain cancer, Hodgkin lymphoma, non-Hodgkin lymphoma, renal tumors, neuroblastoma, soft tissue sarcomas, and bone sarcomas. The group was split into three cohorts: 6,193 (26.4%) treated in the 1970s; 9,363 (39.9%) treated in the 1980s; and 7,906 (33.6%) treated in the 1990s. Median age at diagnosis was 6.1 years (range 0-20.9), and at last follow-up, 27.7 years (8.2-58.3). A comparison group of 5,057 siblings of cancer survivors were also included.

Cumulative incidence and 95% confidence intervals were measured for reported heart failure, coronary artery disease, valvular heart disease, pericardial disease, and arrhythmias by treatment decade.The 20-year cumulative incidence of heart failure and coronary artery disease decreased in more recent eras ($p < 0.01$), although not valvular disease, pericardial disease, or arrhythmias. Compared with survivors with a diagnosis in the 1970s, the risk of heart failure, coronary artery disease, and valvular heart disease decreased in for those diagnosed in the 1980s and 1990s, but the decrease was only significant for those with coronary artery disease.

Editor's Note: *Historic reductions in exposure to cardiac radiation have been associated with reduced risk of coronary artery disease among adult survivors of childhood cancer. This bodes well for these individuals when they seek insurance in adulthood. However, additional studies are needed to investigate risk reductions for other cardiac outcomes.*

MEDICAL TEAM UPDATE

RGA's U.S. Mortality Markets team welcomes two new doctors:
Maryam B. Shapland, M.D., DBIM, and **Preeti Dalawari, M.D., MSPH**. Dr. Shapland, Vice President and Medical Director, is based in the Bay Area in California, and her specialties are emergency medicine and insurance medicine. Dr. Dalawari, Medical Director, is based in St. Louis. Her medical specialty is emergency medicine, and her MSPH is in epidemiology.

RECENT WEBCASTS

RGA's most recent webcasts, available for viewing at your convenience, focus on topics of interest to underwriters, claims managers, and insurance medical directors.

Modeling Infectious Disease Outbreaks 2020
Eric Westhus, Ph.D., Data Scientist, Global Research and Data Analytics, RGA (running time: 13:20)
https://www.rgare.com/knowledge-center/media/videos/modelling-infectious-disease-outbreaks

Modeling is a highly complex segment of data science, but Dr. Westhus successfully breaks down the concepts underlying modeling for infectious disease outbreaks in clear, understandable language, providing insight into how the current COVID-19 pandemic is progressing.

Opioid Mortality Trends: Considerations for Insurers
Vincent Prange, Actuarial Assistant, Global Research and Data Analytics, RGA (running time: 7:16)
https://www.rgare.com/knowledge-center/media/videos/opioid-mortality-trends-considerations-for-insurers

Over the past decade, mortality related to synthetic and prescription opioids has been on the rise. For specific segments, especially the insured, trends show some heterogeneity. This video discusses aspects of research conducted by RGA into opioid-related mortality by segment and offers insights for insurers to consider.

Opioid Prescription: History Analysis
Nick Kocisak, Senior Actuarial Assistant, Global Data and Research Analytics, RGA (running time: 13:00)
https://www.rgare.com/knowledge-center/media/videos/opioid-prescription-history-analysis

Opioid mortality risk is impacted by the type of opioid prescribed, the duration of the prescription, and possible interaction with benzodiazepines. This webcast outlines and explains our insights into the relationships discovered in RGA's research into opioid-related mortality.

RGA THOUGHT LEADERSHIP PUBLICATIONS

RGA publishes content on many topics of interest to insurers. Here are links to some recent publications:

SPECIAL FEATURE: Today's Challenges in Infectious Disease
An interview with Michael T. Osterholm, Ph.D., MPH, Regents Professor, McKnight Presidential Endowed Chair in Public Health, and Director, Center for Infectious Disease Research and Policy (CIDRAP), University of Minnesota.
Note: *This interview, published in the Jan 2020 issue of* ReFlections*, was conducted in 4Q 2019, before the COVID-19 pandemic, and remains highly relevant.*
https://www.rgare.com/knowledge-center/media/articles/today's-challenges-in-infectious-disease

Depression: Key Points for Accurate Underwriting
By Akhilesh Pandey, Senior Underwriter, Research and Manual Development, RGA India
https://www.rgare.com/knowledge-center/media/articles/depression-key-points-for-accurate-underwriting

The Expanding Diabetes Classification Matrix: Types 1, 2, and More
By Dr. Karneen Tam, Medical Consultant, RGA Asia
https://www.rgare.com/knowledge-center/media/articles/the-expanding-diabetes-classification-matrix-types-1-2-and-more

The HIV/AIDS Epidemic – What's New? Pre-Exposure Prophylaxis (Part II)
By Dr. John J. Lefebre, FRCPC, Medical Consultant, RGA
https://www.rgare.com/knowledge-center/media/research/the-hiv-aids-epidemic-what-s-new-pre-exposure-prophylaxis-(prep)-(part-ii)

"Webside" Manner: The Promise and Perils of Telemedicine
By Dr. Dennis Sebastian, Regional Director, Health, RGA Middle East
https://www.rgare.com/knowledge-center/media/articles/webside-manner-the-promise-and-perils-of-telemedicine

Opioid Misuse and Mortality Risk
By Julianne Callaway, FSA, ACAS, MAAA, Vice President and Actuary, Strategic Research, Global Research and Data Analytics (GRDA); Nick Kocisak, Senior Actuarial Assistant, GRDA; Vincent Prange, Actuarial Assistant, GRDA; Kristen Kenney, Senior Actuarial Assistant, GRDA; Kyle Nobbe, FSA, MAAA, Actuary
https://www.rgare.com/knowledge-center/media/research/opioid-misuse-and-mortality-risk

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